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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/559,595
Filing Date: November 30, 2005
Appellant(s): ONG ET AL.

RICHARD SAN PIETRO
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 18, 2009 appealing from the Office action mailed February 20, 2009.

(1) Real Party in Interest

The real party in interest in the case is Amylin Pharmaceuticals, Inc., the assignee of record.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

US 2002/000949	ROTHBARD	1-2002
WO 02/098348	DEFELIPPIS	12-2002
US 2003/0087820	YOUNG	5-2003
US 5,330,761	BAICHWAL	7-1994
US 4,847,240	RYSER	7-1989

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Rothbard et al (US 2002/0009491 A1).

Rothbard et al teach a pharmaceutical composition comprising components (delivery-enhancing transporter (poly-arginine) and biologically active agents (such as peptide or protein)) in a suitable medium, such as water or a buffered aqueous solution (see paragraphs [0026], [0038] and [0123]). Since the bioactive peptide and cationic polyamino acid are formed in water or aqueous buffer, this would inherently have the functionality and the characteristics of the instantly claimed invention.

Claims 1-4, 6-7, 9-10, 15-16 and 18-21 are rejected under 35 U.S.C. 102(a) as being anticipated by Defelippis et al (WO 02/098348, filed in the IDS).

15. Defelippis teaches a composition comprising a GLP-1 compound and a basic polypeptide (see claim 1). Defelippis specifically teaches the use of exendin-4 (see claim 8, page 12, lines 6-21) as the GLP-1 compound. Defelippis teaches polyarginine as the basic polypeptide (see claim 13). Further, Defelippis teaches that the composition is in a buffered solution (see page 27, lines 18-20) and teaches solutions for injection (see page 31, lines 7-10). This meets the limitation of claims 1, 7 and 9-10. Defelippis teaches the use of a zinc solution at pH of between about 5 and about 6 (see page 29, lines 29-32) and also teaches pH adjustments to less than 5 (see page 31, lines 14-15) and the use of an acetate buffer (see page 29, lines 23-24), meeting the limitations of claims 2-4. Further, Defelippis teaches that use of sucrose (see page 33, line 2) in the composition, meeting the limitation of claim 15. Additionally, Defelippis

teaches the use of starch (see page 35, line 1) in the composition, and the use of phenol (see page 31, line 1) and the use of in the composition, meeting the limitations of claims 6, 16 and 18. The instant specification discloses that "exemplary viscosity-increasing and bioadhesive agents that may be used in the compositions discloses herein, include, but are not limited to cellulose derivatives...starch, gums, carbomers, and polycarbophil..." (see paragraph [0210] of instant specification US 2006/0172001 A1). Since bioadhesive includes starch, which is disclosed by Defelippis reference, this meets the limitation of claim 6. Since the reference teaches the composition comprising poly-arginine peptide, exendin-4, and buffer at pH of the instant claims, the composition would inherently have the same functionality and characteristics as the instant composition. Therefore, the composition of the reference would increase the absorption by at least 2 fold, at least 5 fold, and at least 10 fold, meeting the limitations of claims 19-21. Therefore, Defelippis meets the limitations of claims 1-4, 6-7, 9-10, 15-16 and 18-21 of the instant claims.

Claims 1-4, 6-7, 9-10, 15-16 and 18-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Defelippis et al (WO 02/098348).

The teachings of Defelippis are described, supra. Therefore, Defelippis teachings meet the limitations of claims 1-4, 6-7, 9-10, 15-16 and 18-21 of instant application.

35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 15-26 rejected under 35 U.S.C. 103(a) as being unpatentable over Young et al (US 2003/0087820 A1, filed in the IDS) in view of Baichwal AR (US Patent No. 5,330,761) and Ryser et al (US Patent No. 4,847,240, filed in the IDS).

Young discloses a pharmaceutical composition for using exendin-4 for transmucosal administration (see paragraph [0188]) using an acetate/glutamate buffer (comprises acetic acid/glutamic acid), with a pH in the range of 3-7 (see paragraph [0203]) and further ingredients including mannitol (tonicifying agent), m-cresol (preservative), methylcellulose (viscosity-increasing agent) and other excipients as needed, such as sodium chloride (see paragraph [0203]). Young teaches that the dosage forms preferably include approximately 0.005 to about 5%, of the active ingredient in an aqueous system along with approximately 0.02 to 0.5% (w/v) of an acetate, phosphate, citrate or glutamate or similar buffer either alone or in combination to obtain a pH of the final composition of approximately 3.0 to 7.0 (see paragraph [0203]). This meets the limitation of claims 1-5, 6 in part, 9-10, 15-16, 18-24 and 26. The difference between the reference and the instant claims is that the reference does not teach a bioadhesive agent and the polyarginine and the range of molecular weights of the polyamino acids, tonicifying agent, viscosity-increasing agent, bioadhesive agent and preservative (Young's ranges overlap the instantly claimed ranges).

However, Baichwal AR teaches that a bioadhesive controlled-release solid dosage forms adhere to mucosa (especially in the oral cavity, but also e.g. in periodontal pockets, surgical wounds etc) to provide controlled release of analgesics, anti-inflammatories, anti-tussives, hormone, antibiotics, etc. Further, Baichwal teaches that the bioadhesive controlled release excipients are directly compressible into tablet formulations which are not absorbed into body but provides a localized effect (see basic abstract enclosed).

Further, Ryser teaches that it is well known that many molecules of a wide variety are not transported, or are poorly transported, into living cells. Macromolecules, for example, such as proteins, nucleic acids, and polysaccharides are not suited for diffusion or active transport through cell membranes simply because of their size (see column 1, lines 22-27). Ryser teaches that cationic polypeptides, and in particular polyarginine effect or enhance cellular uptake of molecules which are either excluded from or are poorly taken up by cells (see column 1, lines 48-65 and column 4, lines 12-12-18). Ryser teaches that for some proteins as much as a factor of several hundred fold and dramatically increases cellular transport of molecules such as drugs co-factors nucleotides and nucleotide analogs, gaining a very important advantage by using selected cationic polymers, such as poly-L-lysine and poly-L-arginines, which are excellent substrates for physiological proteolytic enzymes present in mammalian cells, i.e. after having served as a transport carrier, they can be digested or otherwise broken down inside the cells into normal physiologic by-products (see columns 3-4, specifically, column 4, lines 29-34). Ryser further discloses that there are wide variety of molecules which can be covalently bonded to cationic polymers including, peptides and that typically the positively charged groups are primary, secondary, or tertiary amines which ionize at or around neutral pH (the range claimed to prevent precipitation), and that cationic poly(amino acids) are preferred because of the outstanding enhancement in cellular uptake which they provide along with the digesting by proteolytic enzyme some poly(amino acid), i.e. polyarginine, provide (see columns 5-6). Ryser teaches that polycationic amino acids have multiple uses including chemotherapeutic applications,

anti-microbial application, for genetic diseases, enhancing cellular uptake or polypeptide hormones, such as insulin, cellular transport for other molecules having biological functions (see columns 15-16).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Young, Baichwal and Ryser for the express benefits for enhancing cellular uptake of polypeptide hormones across membranes, for controlled release, and for the adhesion of the bioactive agents to the mucosa of the patient population (oral cavity, etc). Young reference indicates that delivery of peptide drugs is often difficult because of factors such as molecular size, susceptibility to proteolytic breakdown, rapid plasma clearance, peculiar dose-response curves...and the tendency of peptides and proteins to undergo aggregation, adsorption, and denaturation. Thus, there continues to exist a need for the development of alternative methods to the inconvenient, sometimes painful, injection for administration of peptide drugs (i.e., better transmucosal routes of administration is necessary because the properties of peptides and proteins make them difficult to utilize) (see paragraph [0009]). One of ordinary skill in the art would have been motivated to combine the teachings since Ryser teaches that cationic polypeptides (polyarginines) enhance the cellular uptake of molecules which are either excluded from or are poorly taken up by cells (some proteins as much as by a factor of several hundred fold and dramatically increased cellular transport of molecules), and Baichwal teaches that addition of bioadhesive enhances the controlled release and adhesion of the bioactive molecules to the mucosa. There is a reasonable expectation of success, since Ryser teaches the enhancing the cellular uptake of

protein hormones or polypeptide hormones, such as insulin, and Baichwal teach the controlled release and mucosa adhesion of wide variety of different types of drugs, including analgesics, anti-inflammatory agents, anti-tussive agents, hormone, antibiotics, antacids, anti-viral agents, etc (see claim 3).

Furthermore, in regards to the ranges, the MPEP states the following: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 (“*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.*”); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc.

v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. Denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Therefore, there is a motivation to optimize since the normal desire of scientist is to improve upon what is already known through routine optimization, with the reasonable expectation that optimization of the known ranges would at least lead to a optimal compound that would lead to optimal treatment conditions.

35 U.S.C. 112, 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 15-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites, "...wherein at the pH of the composition said compatible buffer does not cause precipitation of the cationic polyamino acid, and has a mono-anionic or neutral net charge; and wherein the bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition..." It is unclear how a bioactive peptide or protein of interest will have the same net charge as the cationic polyamino acid. For example, if the poly-arginine is a 13mer, this would give a net charge of +13. It is unclear how a bioactive peptide or protein, exendin-4, having a 39 amino acid would have a net charge of +13. The sequence of exendin-4 is

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS. There are not enough positively charged amino acids (K, R and H) to get the same net charge of +13 as the cationic polyamino acid. Furthermore, it is unclear how a cationic polyamino acid would have a mono-anionic charge or a neutral net charge, when the cationic amino acid would have a + charge. Because claims 2-10, 15-21 depend from indefinite claim 1 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 22 recites, "...said compatible buffer does not cause precipitation of the cationic polyamino acid and has a mono-anionic or neutral net charge; and wherein the bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition..." It is unclear how a bioactive peptide or protein of interest will have the same net charge as the cationic polyamino acid. For example, if the poly-arginine is a 13mer, this would give a net charge of +13. It is unclear how a bioactive peptide or protein, exendin-4, having a 39 amino acid would have a net charge of +13. The sequence of exendin-4 is

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS. There are not enough positively charged amino acids (K, R and H) to get the same net charge of +13 as the cationic polyamino acid. Furthermore, it is unclear how a cationic polyamino acid would have a mono-anionic charge or a neutral net charge, when the cationic amino acid would have a + charge. Because claims 23-26 depend from indefinite claim 22 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 27 recites, "...wherein the extendin-4 has the same net charge as the poly-arginine at the pH of the composition." It is unclear how a bioactive peptide or protein of interest will have the same net charge as the cationic polyamino acid. For example, if the poly-arginine is a 13mer, this would give a net charge of +13. It is unclear how a bioactive peptide or protein, extendin-4, having a 39 amino acid would have a net charge of +13. The sequence of extendin-4 is HGEFTFTSDLKQMEEEAVRLFIEWLKNGGPSSGAPPPS. There are not enough positively charged amino acids (K, R and H) to get the same net charge of +13 as the cationic polyamino acid. Because claims 28-30 depend from indefinite claim 27 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 31 recites, "...wherein the extendin-4 has the same net charge as the poly-arginine at the pH of the composition." It is unclear how a bioactive peptide or protein of interest will have the same net charge as the cationic polyamino acid. For example, if the poly-arginine is a 13mer, this would give a net charge of +13. It is unclear how a bioactive peptide or protein, extendin-4, having a 39 amino acid would have a net charge of +13. The sequence of extendin-4 is HGEFTFTSDLKQMEEEAVRLFIEWLKNGGPSSGAPPPS. There are not enough positively charged amino acids (K, R and H) to get the same net charge of +13 as the cationic polyamino acid. Because claims 32-34 depend from indefinite claim 31 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

(10) Response to Argument

Appellant's Arguments

In regards to rejection under 35 U.S.C. 112, second paragraph, Appellant argues that "it appears that the rejection is not based on a proper interpretation of this claim term." Appellant argues that "at paragraph 23 of the specification (p. 8, lines 16-20) states...it is not necessary that the magnitude of the charge be identical, but only that the net charge be the same...when the claims are properly interpreted in view of the specification and using proper legal precedent, it is clear that the claims are not indefinite." In regards to claim 31, Appellant further argues that "It is noted that the pH recited in claim 31 is 4.5, at which pH the charge groups such as arginine, lysines, and histidines will be protonated, giving the peptide a net positive charge, since the pI of exendin-4 is 5.3. Thus, at such pH the bioactive peptide and cationic polyamino acid have the same net charge, and the claim is not unclear of indefinite."

In regards to rejection of claim 1 under 35 U.S.C. 102(b) anticipated by Rothbard, Appellant argues that "Rothbard does not disclose a composition where the bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition...Rothbard explains at paragraph 44 (and 45) that the components of the composition (delivery-enhancing transporters such as poly-Arg (paragraph 48), and the biologically active agent (paragraph 26)) 'are held in an ionic association, typically viewed as an ion pair' Thus, these components of an ion pair necessarily have opposite net charges at the pH of the composition, one net positive and the other net negative."

In regards to rejection of claims 1-4, 6-7, 9-10, 15-16 and 18-21 under 35 U.S.C. 102(a) and (e) over Defelippis, Appellant argues that “the present claims recite that the bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition. The disclosure of Defelippis makes it clear that the bioactive peptide or protein of interest and the cationic polyamino acid disclosed have opposite charges, and cannot have the same net charge...Defelippis et al disclose that their formulation is comprised of particles of GLP-1 complexed with a basic polypeptide, such as polylysine, polyarginine, etc. Thus, the complex is present in a solid form and held together by an ionic bond. Therefore, it is necessarily the case that the GLP-1 and polypeptide have opposite net charge, or they could not be held together in an ionic bond.” Appellant further argues that “the present claims recite that the pharmaceutical composition has a pH at which the compatible buffer does not cause precipitation of the cationic polyamino acid. Defelippis discloses a composition at a pH where the GLP-1 and polyamino acid is precipitated, since it is disclosed as being in particle form (p. 5, lines 1-6, p. 41, Example 4), whereas the present claims require that the buffer ‘does not cause precipitation of the cationic polyamino acid.’”

In regards to rejection of claims 1-10 and 15-26 under 35 U.S.C. 103(a) over Young (US 2003/0087820) in view of Baichwal (US Patent No. 5,330,761) and Ryser (US Patent No. 4,847,240), Appellant argues that “Young discloses a liquid formulation comprising exendin, acetate buffer, mannitol as an iso-osmolality modifier. Young does not disclose a cationic polyamino acid at all, nor that the cationic polyamino acid has the same net charge as the peptide or protein of interest...Baichwal is not properly

combinable with Young. Baichwal discloses a tablet containing an active ingredient that is not absorbed into the body but instead provides a localized effect...Modifying Young according to Baichwal changes the principle of operation of Young, and the two references are not properly combinable...Ryser discloses that the cellular uptake of some molecules could be improved by the simple presence in the experimental medium of cationic polymers. Ryser make no disclosure on how to transport material across a mucous membrane to achieve transmucosal absorption...Young is concerned with the introducing extendin into the blood plasma...But Ryser functions according to a principle of cellular uptake through diffusion or active transport to achieve a localized affect, and not systemic effect. The person of ordinary skill in the art finds no reason that a method of increasing active transport or diffusion into a cell would have any effect on increasing the concentration of a peptide in the bloodstream." Appellant further argues that "the rejection appears to be based solely on impermissible hindsight and is made only by using the claims as a blueprint, and by selecting portions of the prior art to thereby form the rejection."

Response to Arguments

Concerning Appellant's argument that "it appears that the rejection is not based on a proper interpretation of this claim term." Appellant argues that "at paragraph 23 of the specification (p. 8, lines 16-20) states...it is not necessary that the magnitude of the charge be identical, but only that the net charge be the same, it is still unclear how the peptide and the polyamino acid can one can reach the same net charge regardless of

their magnitude. Again, there are not enough charged amino acids to reach a net charge that equals mono-anionic or neutral net charge, and be the same as the polyamino acids. Therefore, the claims are still indefinite. Furthermore, net charge implies the total charge present in the composition. Thus, for example, when there are 13 arginines in the polyamino acids, it is unclear how a protein or polypeptide can have the same net charge as the polyamino acids. The specification does not fully define what a net charge is referring to. Concerning claim 31, Appellant argues that "It is noted that the pH recited in claim 31 is 4.5, at which pH the charge groups such as arginine, lysines, and histidines will be protonated, giving the peptide a net positive charge, since the pI of exendin-4 is 5.3." Exendin-4 has the sequence **HGEGTFTS~~DL~~SKQMEEEAVRLFIEWLKNGGPSSGAPPPS**. There are 4 (H, K, R) positively charged amino acids and 6 (E and D) negatively charged amino acids. This would give a net charge of -2, which is not the same as polyamino acids. Therefore, it is still unclear how the two can have the same net charge. Therefore, claims 1-10, 15-34 are indefinite.

Concerning Rothbard reference, Claim 1 recites, "...wherein at the pH of the composition said compatible buffer does not cause precipitation of the cationic polyamino acid and has a mono-anionic or neutral net charge...wherein the bioactive peptide or protein of interest has the same net charge as the cationic polyamino acid at the pH of the composition..." A mono-anionic charge would leave a -1 charge. A neutral net charge would leave a charge of "0". Rothbard reference teaches all of the active components recited in the instant claim 1. Rothbard teaches biologically active protein

(delivery-enhancing transporter (poly-arginine) and biologically active agents (such as peptide or protein)) in a suitable medium, such as water or a buffered aqueous solution (see paragraphs [0026], [0038] and [0123]). Since the bioactive peptide and cationic polyamino acid are formed in water or aqueous buffer, this would inherently have the functionality and the characteristics of the instantly claimed invention. The MPEP § 2112 states: "Once a reference teaching product appearing to be substantially identical is made the basis of a rejection, and the Examiner presents evidence or reasoning tending to show inherency, the burden shifts to the Applicant to show an unobvious difference '[t]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on *prima facie* obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977))." The reference teaches all of the active components of the instant claim 1.

Concerning DeFilippis reference teaches a composition comprising exendin-4 with basic polypeptides, such as polylysine, polyarginine, polyornithine or others (see p. 5, lines 1-6). Defelippis reference teaches a composition at the same pH (about pH 5.0 to about 6.0 and below 5.0) comprising poly-arginine and Exendin-4 and the use of acetate buffer. Since the reference teaches the composition comprising the same components as the instant claims, the composition would inherently have all of the

functionality and characteristics as the instantly claimed pharmaceutical composition. Further, the bioactive peptide (exendin-4) would have the same net charge as the cationic polyamino acid at the pH of the composition. The reference teaches that the amount of the exendin solution and the basic peptide solution can be mixed together, may be adjusted on the concentration of the therapeutic peptide compound and the basic polypeptide and the buffered zinc acetate or zinc chloride solution is at pH of between about 5 and about 6 can be added to the peptide/basic polypeptide suspension (see p. 29, lines 29-32 and p. 31, lines 14-15). The reference teaches the same composition in the same pH range as instant claims, therefore, the composition inherently has the same characteristic as the instant claims. Additionally, the reference teaches exendin-4 (see SEQ ID NO: 2, p. 12) and preparation of the particles in a suspension (see p. 26, for example). Furthermore, the reference teaches that "the suspension can be manipulated to form a solution which can then be administered as an injectable composition or as an aerosol or spray-dried to a dry powder composition of particles. If a solution is desired, the suspension of particles can be dissolved by adjusting the pH of the suspension...adjustment of the pH to less than 6 will result in dissolution of the particles. More preferred is a pH of less than 5. Most preferred is a pH less than 4...the solution described herein can be used or adapted for use as a composition delivered as an aerosol through the pulmonary route..." (see p. 31, lines 7-24). Again, the reference teaches all of the components of the instant claims at the same pH as claimed. Therefore, the reference anticipates the instant claims 1-4, 6-7, 9-10, 15-16 and 18-21.

Concerning the 35 U.S.C. 103(a) rejection, Young reference discloses a pharmaceutical composition for using exendin-4 for transmucosal administration (see paragraph [0188]) using an acetate/glutamate buffer (comprises acetic acid/glutamic acid), with a pH in the range of 3-7 (see paragraph [0203]) and further ingredients including mannitol (tonicifying agent), m-cresol (preservative), methylcellulose (viscosity-increasing agent) and other excipients as needed, such as sodium chloride (see paragraph [0203]). It was indicated in the body of the rejection that difference between the reference and the instant claims is that the reference does not teach a bioadhesive agent and the polyarginine and the range of molecular weights of the polyamino acids, tonicifying agent, viscosity-increasing agent, bioadhesive agent and preservative (Young's ranges overlap the instantly claimed ranges). Baichwal teaches a bioadhesive controlled-release solid dosage forms adhere to mucosa (especially in the oral cavity, but also e.g. in periodontal pockets, surgical wounds etc) to provide controlled release of analgesics, anti-inflammatories, anti-tussives, hormone, antibiotics, etc. Ryser teaches the function of cationic polypeptides that increases the cellular uptake of the therapeutic molecules. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings and formulate a therapeutic composition for enhanced delivery of the therapeutic agent by associating the agent to a component that enhances the cellular uptake of the agent that is also digested *in vivo*. Young teaches a transmucosal administration and Baichwal teaches an adhesive used for mucosal membrane, therefore, one of ordinary skill in the art would have been motivated to try the combination of the two, for the same purpose of delivering the

therapeutic composition via transmucosal administration. Both Young and Baichwal teach mucosal delivery, therefore, the prior arts are combinable. Modifying Young would not change the principal operation of Young, since Baichwal also teaches mucosal delivery. Baichwal AR teaches that a bioadhesive controlled-release solid dosage forms adhere to mucosa to provide controlled release of analgesics, anti-inflammatories, anti-tussives, hormone, antibiotics so one of ordinary skill in the art would be motivated to add the bioadhesive for controlled release of the therapeutic agent for mucosal delivery.

Furthermore, since Young teaches a transmucosal administration, one of ordinary skill in the art would have been motivated to combine the teachings of Young and Ryser for enhancing the cellular uptake of the therapeutic agent via transmucosal administration. Ryser teaches that the that cationic polypeptides, and in particular polyarginine effect or enhance cellular uptake of molecules which are either excluded from or are poorly taken up by cells (see column 1, lines 48-65 and column 4, lines 12-12-18). Ryser teaches that for some proteins as much as a factor of several hundred fold and dramatically increases cellular transport of molecules such as drugs co-factors nucleotides and nucleotide analogs, gaining a very important advantage by using selected cationic polymers, such as poly-L-lysine and poly-L-arginines, which are excellent substrates for physiological proteolytic enzymes present in mammalian cells, i.e. after having served as a transport carrier, they can be digested or otherwise broken down inside the cells into normal physiologic by-products. Since Ryser teaches that cationic polypeptides enhance the cellular uptake of the therapeutic agent dramatically, and are digested by the enzymes present in the mammalian cells, one would be

motivated to try adding the cationic polypeptides to enhance delivery of the therapeutic agents to the cells. Furthermore, one of ordinary skill in the art would have been motivated to combine the teachings and adapt the teachings for the current purpose in view of current teachings in pharmaceutical formulations. Therefore, the combined prior arts are *prima facie* obvious over the instant claims.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Julie Ha/

Examiner, Art Unit 1654

Conferees:

/Cecilia Tsang/

Supervisory Patent Examiner, Art Unit 1654

/Michael G. Wityshyn/

Supervisory Patent Examiner, Art Unit 1651

